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Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs

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Abstract

The main purpose of this work is to prepare self-microemulsifying drug delivery system (SMEDDS) for oral bioavailability enhancement of a poorly water soluble drug, simvastatin. Solubility of simvastatin was determined in various vehicles. SMEDDS is mixture of oils, surfactants, and cosurfactants, which are emulsified in aqueous media under conditions of gentle agitation and digestive motility that would be encountered in the gastro-intestinal (GI) tract. Pseudo-ternary phase diagrams were constructed to identify the efficient self-emulsification region and particle size distributions of the resultant microemulsions were determined using a laser diffraction sizer. Optimized formulations for in vitro dissolution and bioavailability assessment were Carpryol 90 (37%), Cremophor EL (28%), and Carbitol (28%). The release rate of simvastatin from SMEDDS was significantly higher than the conventional tablet. The prepared SMEDDS was compared with the conventional tablet (Zocor®) by administering the prefilled hard capsules to fasted beagle dogs. The absorption of simvastatin acid from SMEDDS form resulted in about 1.5-fold increase in bioavailability compared with the conventional tablet. Our studies illustrated the potential use of SMEDDS for the delivery of hydrophobic compounds, such as simvastatin by the oral route.

Keywords: Self-emulsifying drug delivery system; Simvastatin; Microemulsion; Bioavailability

1. Introduction

Simvastatin was a cholesterol-lowering agent widely used to treat hypercholesterolemia. Simvastatin, an inactive lactone, is converted to corresponding β,δ-dihydroxy acid in liver by cytochrome-3A after oral administration. Simvastatin is a potent inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which was an early and rate-limiting step in the biosynthesis of cholesterol (Cheng et al., 1993; McClelland et al., 1991). Simvastatin, crystalline powder with a melting point of 135–138 °C, is practically insoluble in water and poorly absorbed from the gastro-intestinal (GI) tract.

It has been focused on enhancing the solubility of poorly water soluble drugs and improving bioavailability to administer them through oral route resulting

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in increasing their clinical efficacy. One of the most popular approach is the incorporation of the active lipophilic component into inert lipid vehicles (Aungst, 1993), such as oils (Burcham et al., 1997), surfactant dispersions (Serajuddin et al., 1988), self-emulsifying formulations (Charman et al., 1992; Craig et al., 1993; Shah et al., 1994; Wakerly et al., 1986), emulsions (Kararli et al., 1992; Myers and Stella, 1992; Palin et al., 1986; Stella et al., 1978; Toguchi et al., 1990), and liposomes (Schwendener and Schott, 1996).

Among of these approaches, self-microemusifying drug delivery system (SMEDDS) was used for lipophilic drug which is associated with poorly water solubility and low bioavailability after the oral delivery. SMEDDS is isotropic mixtures of an oil, surfactant, cosurfactant (or solubilizer), and drug. The basic principle of this system is its ability to form fine oil-in-water (o/w) microemulsions under gentle agitation following dilution by aqueous phases. That is the digestive motility of the stomach and intestine providing the agitation required for self-emulsification in vivo (Constantinides, 1995; Shah et al., 1994). The spontaneous formation of an emulsion upon drug release in the GI tract advantageously presents the drug in a dissolved form and the small droplet size provides a large interfacial surface area for drug absorption (Charman et al., 1992; Shah et al., 1994). For selecting a suitable self-emulsifying vehicle, it is important to assess; (a) the drug solubility in various components, (b) the area of self-emulsifying region in the phase diagram, and (c) droplet size distribution following self-emulsification (Kommuru et al., 2001). In this study, various types of self-emulsifying formulations were prepared using four oils (Capryol 90, Lauroglycol 90, Labrafil M 1944 CS, and Labrafil M 2125), two surfactants (Cremophor EL and Tween 80), and four cosurfactant (Carbitol, PEG 400, polypropylene glycol, dimethyl ether isosobide).

The objectives of this study were to develop and characterize the optimal formulation of SMEDDS containing simvastatin and to assess its bioavailability compared with a simvastatin tablet (Zocor®, simvastatin 20 mg) in beagle dogs. Mean particle size of microemulsion was conducted by dynamic light scattering (DLS). The in vitro release profiles of simvastatin from SMEDDS and the conventional tablet were compared by high performance liquid chromatography (HPLC).

2. Materials and methods

2.1. Materials

Simvastatin base was purchased from McFarland Smith (Edinburgh, UK). Diethylene glycol monoethyl ether (Carbitol) was purchased from TCI (Tokyo, Japan), polyglycolysed glycerides (Labrasol, Labrafill M 1944 CS, Labrafill M 2125, Labroglycol 90, and Capryol 90) were obtained from Gattefosse (Westwood, NJ, USA). Cremophor EL and C-18 solid-phase extraction cartridges were purchased from BASF (Germany) and Phenomenex® (Strata, USA), respectively. Deionized water was prepared by a Milli-Q purification system from Millipore (Molsheim, France). Acetonitrile and methanol (HPLC grade, Burdick & Jackson, USA) were used in the present study. All other chemicals were reagent grade.

2.2. Solubility studies

The solubility of simvastatin in various oils, surfactants, and cosurfactants was determined, respectively. 2 ml of each of the selected vehicle were added to each cap vial containing an excess of simvastatin (ca. 500 mg). After sealing, the mixture was heated at 40 °C in a water-bath to facilitate the solubilization using a vortex mixer. Mixtures were shaken with shaker at 25 °C for 48 h. After reaching equilibrium, each vial was centrifuged at 3000 rpm for 5 min, and excess insoluble simvastatin was discarded by filtration using a membrane filter (0.45 μm, 13 mm, Whatman, USA). The concentration of simvastatin was quantified by HPLC.

2.3. Pseudo-ternary phase diagram study

The pseudo-ternary phase diagrams of oil, surfactant:cosurfactant, and water were developed using water titration method: the mixtures of oil and surfactant/cosurfactant at certain weight ratios were diluted with water in a dropwise manner. For each phase diagrams at a specific ratio of surfactant/cosurfactant, 1:0.5, 1:1, 1:2, and 1:3 (w/w), transparent and homogenous mixture of oil and drug was formed under the mixing by magnetic stirring. Then, each mixture was titrated with water and visually observed for phase clarity and flow ability. After the identification

of microemulsion region in the phase diagrams, the microemulsion formulations were selected at desired component ratios. In order to form the microemulsion, a series of SMEDDS were prepared as following.

2.4. Preparation of SMEDDS

A series of SMEDDS were prepared in each of five formulations (Table 2) with varying ratio of oil, surfactant, cosurfactant, and simvastatin. In all the formulations, the level of simvastatin was constant (i.e. 6.98% (w/w) of the vehicle) except SMEDDS D-form (i.e. 13.04% (w/w) of the vehicle). Briefly, simvastatin was dissolved by cosrufactant, such as Carbitol in glass vials. Oil and surfactant were accurately weighed into glass vials. Then, the components were mixed by gentle stirring and vortex mixing, and heated at 37 °C in incubator, until simvastatin perfectly has dissolved. The mixture was stored at room temperature until used.

2.5. Emulsion droplet size analysis

SMEDDS (50 μl) was diluted with water (50 ml) in a volumetric flask and gently mixed by inverting the flask. The droplet size distributions of resultant emulsions were determined after 1 h by DLS (ELS-8000, Potal, Japan).

2.6. In vitro dissolution test

The quantitative in vitro release test was performed in 900 ml of simulated intestinal fluid (pH 1.2), which was based on USP 24 method (Dissolution apparatus #2, at 100 rpm). SMEDDS (simvastatin 20 mg) was placed in the dialysis bag (MWCO 12,000 g/mole; Spectrum, USA) during the release period to compare the release profile with the conventional tablet (Zocor®, simvastatin 20 mg). During the release studies, 1 ml of sample of simulated intestinal fluid was taken out and kept in amber autosample vial following the initiation of test. All samples were analyzed with HPLC.

2.7. HPLC analysis of simvastatin

The concentration of simvastatin in the samples was determined by HPLC analysis. The HPLC analysis system consisted of tsp-P2000 pump, tsp-UV2000 ultraviolet detector, and tsp-AS3000 autosampler. The chromatographic column was a Fluofix 12W425 4.6 mm × 250 mm (Neos, Japan) and the guard column 1EWDG1 4 mm × 10 mm (Neos). A mobile phase of acetonitrile:water (40:60) was pumped isocratically at a flow rate of 1.2 ml/min. A 20 μl volume was injected onto the column and the effluent was monitored at 238 nm.

2.8. Bioavailability studies

Nine male beagle dogs, weighing between 10.20 and 12.20 kg (mean±S.D., 10.99±0.87 kg), were used in the study. They were starved for 24 h prior to the experiment. To minimize individual variance and administration time's difference and remove a carryover effect of post drug, animals were allocated at random to three treatment groups. Nine dogs were administered Zocor® tablet (generic simvastatin oral formulation single dose 20 mg), SMEDDS A-form (20 mg single dose orally, mean particle size: 33 nm), and SMEDDS D-form (20 mg single dose orally, mean particle size: 150 nm) in a crossover design. SMEDDS form was administered with hard capsule dosage form. Three periods of experiment were performed. According to half-life of simvastatin, the wash-out periods between the doses were kept for 7 days.

Blood samples (4 ml) were collected from a jugular vein of the neck into the non-heparinized tubes at following times; immediately before administration, 0.3, 0.6, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, and 24 h. After collecting, blood samples were coagulated at room temperature and centrifuged at 3000 rpm for 30 min and plasma samples were taken and transferred into cap tubes. Plasma samples were frozen and stored at −20 °C. Frozen plasma samples were thawed in the dark just prior to extraction procedure at room temperature, thoroughly agitated. 100 μl of internal standard (lovastatin acid, 10 μg/ml in acetonitrile:water (60:40, v/v)) was added into 1 ml of plasma and mixed for 30 s. The plasma was transferred to a C-18 Strata™ solid-phase extraction cartridge, which had been activated with 3 ml of methanol and 3 ml of distilled water and mounted on a vacuum manifold system. The extraction cartridge was washed with 3 ml of water. The washing procedure was repeated six times, samples were eluted using two portions of

1 ml methanol. This fraction was evaporated using a speed vacuum concentration (Modul 3180, Hanil, Korea). The samples were reconstituted with 200 μl of acetonitrile:water (60:40, v/v). A 100 μl volume of the eluted fraction was injected onto the HPLC column.

2.9. Analysis of simvastatin and its metabolite (simvastatin acid) in dog plasma

As stock solution, 50 mg simvastatin acid was dissolved in 50 ml solution of acetonitrile:water (60:40, v/v). This solution was diluted in acetonitrile:water (60:40, v/v) at 0.05, 0.1, 0.2, 0.5, and 1 μg/ml for standard solutions. Internal standard, lovastatin acid, was also prepared in acetonitrile:water (60:40, v/v) at 10 μg/ml as same manner. Plasma standards were prepared by the addition of 100 μl of standard solution (each concentration of 0.05–1 μg/ml) and 100 μl of internal standard solution (10 μg/ml) to 0.9 ml of blank plasma. The final concentration of simvastatin acid in the plasma was 0.005, 0.01, 0.02, 0.05, and 0.1 μg/ml. Plasma standards were applied to a C-18 solid-phase extraction column (Strata C18-T, Phenomenex, USA) pre-conditioned with methanol (3 ml) and water (3 ml). The column was washed with water (six times with 3 ml) and dried for 10 min under entirely reduced pressure (67 kPa). Simvastatin acid was eluted with methanol (two times with 1 ml). This extract was evaporated to dry under a stream of nitrogen gas by heating block (35 °C). The residual was reconstituted in 200 μl of acetonitrile:water (60:40, v/v). The resultant was centrifuged at 13,000 rpm for 5 min and the upper fraction was transferred into the tube as an assay sample. A sample (100 μl) was injected onto HPLC.

The HPLC analysis system consisted of tsp-P2000 pump, tsp-UV2000 ultraviolet detector, and tsp-AS3000 autosampler. The chromatographic column was a Fluofix 12W425 4.6 mm × 250 mm (Neos) and the guard column 1EWDG1 4 mm × 10 mm (Neos). A mobile phase of buffer solution of ammonium phosphate:acetonitrile (55:45, v/v) was pumped isocratically at a flow rate of 1.2 ml/min (buffer solution of ammonium phosphate; ammonium phosphate (0.05 M) and phosphoric acid (0.01 M)). A 100 μl volume was injected onto the column and the effluent was monitored at 238 nm.

The mean calibration curve was given by the equation $Y = 6.3482X + 0.0579$ (correlation coefficient $r = 0.9998$), where Y indicates the peak area ratio and X represents the plasma concentration of simvastatin acid.

3. Results and discussion

3.1. Solubility studies

The self-emulsifying formulations consisted of oil, surfactants, cosurfactants, and drug should be a clear and monophasic liquid at ambient temperature when introduced to aqueous phase and should have good solvent properties to allow presentation of the drug in solution. The solubility of simvastatin in various vehicles is presented in Table 1. Capryol 90 and Carbitol provided higher solubility than other vehicles. Capryol 90 and Carbitol as oil and cosurfactant

Table 1
Solubility of simvastatin in various vehicles

Vehicle	Solubility of simvastatin (mg/ml), mean ± S.D.	Vehicle	Solubility of simvastatin (mg/ml), mean ± S.D.
Capryol 90	144.44 ± 4.89	Brij 92	72.33 ± 20.10
Labrafil M 1944 CS	40.96 ± 0.91	Triacetin	39.32 ± 5.23
Labrafac lipophil WL 1349	17.71 ± 0.40	Labrafil M 2125 CS	34.13 ± 3.23
Carbitol	194.35 ± 8.95	Labrasol	76.45 ± 0.31
Tween 60	72.16 ± 2.30	Span 80	52.12 ± 4.30
Tween 80	68.63 ± 1.06	Lauroglycol 90	99.83 ± 5.84
PEG 400	44.08 ± 2.90	Tricaprylin	18.41 ± 0.55
Cremophor EL	70.53 ± 4.60	PEG 200	46.84 ± 3.12
Brij 30	68.04 ± 16.26	Polypropylene glycol	22.11 ± 0.87

was selected, respectively, for the optimal SMEDDS formulation resulting in improved drug loading capabilities.

3.2. Pseudo-ternary phase diagram study

Phase diagrams were constructed in the presence of simvastatin to obtain the optimum concentrations of oil, surfactant, and cosurfactant. SMEDDS form fine oil–water emulsions with only gentle agitation, upon its introduction into aqueous media. Since the free energy required to form an emulsion is very low, the formation is thermodynamically spontaneous (Craig et al., 1995). Surfactants form a layer around the emulsion droplets and reduce the interfacial energy as well as providing a mechanical barrier to coalescence. The visual test is measured the apparent spontaneity of emulsion formation. The series of SMEDDS were prepared and their self-emulsifying properties were observed visually. Pseudo-ternary phase diagrams were constructed to identify the self-emulsifying regions and to optimize the concentration of oil (Fig. 1).

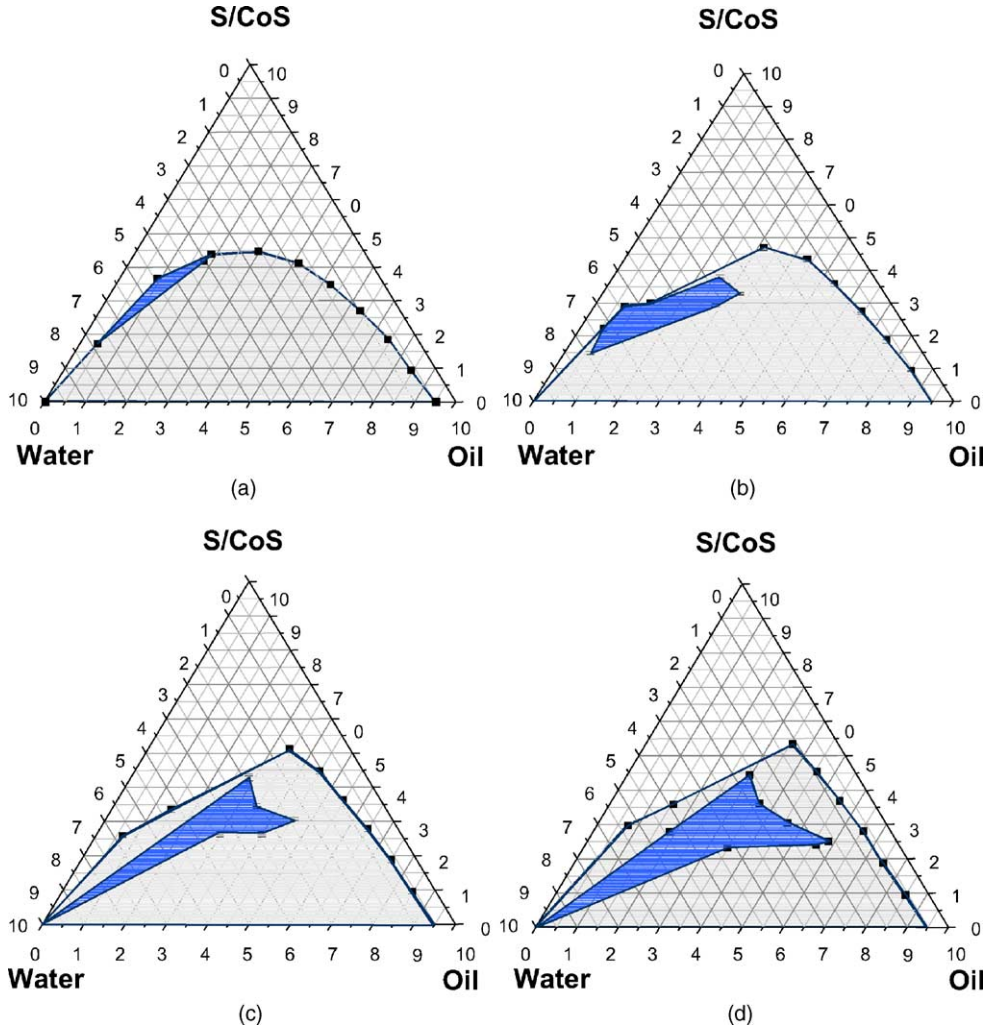

Fig. 1. Pseudo-ternary phase diagrams indicating the efficient self-emulsification region (S/CoS = 1:0.5 (w/w) (a), 1:1 (w/w) (b), 1:2 (w/w) (c), and 1:3 (w/w) (d); the blue area represents o/w microemulsion existence range, the gray area represents coarse emulsion range). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Composition of SMEDDS formulations

Vehicle	Form				
	A	B	C	D	E
Simvastatin	0.3	0.3	0.3	0.6	0.3
Capryol 90	1.6	1.6	1.6	1.6	–
Lauroglycol 90	–	–	–	–	1.6
Carbitol	1.2	–	–	1.2	1.2
PEG 400	–	1.2	–	–	–
Polypropylene glycol	–	–	1.2	–	–
Cremophor EL	1.2	1.2	1.2	1.2	1.2
Mean particle size (nm)	33	176	142	150	766

The efficiency of emulsification was good when the S/CoS concentration was more than 40% of SMEDDS formulation. It was observed that increasing the concentration of the cosurfactant such as Carbitol in SMEDDS formulation increased the spontaneity of the self-emulsification region. Therefore, much higher concentration of cosurfactant, much higher self-emulsifying region in phase diagrams. However, the stability of the self-emulsifying droplets from the ratio of S/CoS = 1:2 and S/CoS = 1:3 (w/w) was decreased because of the precipitation after a few hours. So, the ratio of S/CoS = 1:1 was chosen in the formulation.

3.3. Droplet size analysis

The effect of the formulation of SMEDDS on the droplet size distribution is shown in Table 2. In case of the formulation of SMEDDS containing Capryol 90 as oil, Cremophor EL, such as surfactant, and Carbitol as cosurfactant, the mean droplet size was smaller than the other formulations. Based on the formulation of a stable microemulsion upon exposure to water, the optimized formulations (forms A and D) were developed and their bioavailabilities were compared with the conventional tablet.

The effect of the drug concentration on droplet size in different media; distilled water and simulated gastric fluid (pH 1.2) is represented in Fig. 2. The drug was dissolved in SMEDDS A-form and it was introduced to different media, respectively. The mean droplet size increased with increasing the drug concentration from 2.4 to 18.3%. It could be thought that undissolved drug in the formulation affected the mean droplet size to increase. In case of the same formulation of SMEDDS forms A and D, the mean droplet size of SMEDDS A-form (drug content: 6.98% (w/w) of the vehicle) and D-form (drug content: 13.04% (w/w) of the vehicle) was 33 and 150 nm, respectively.

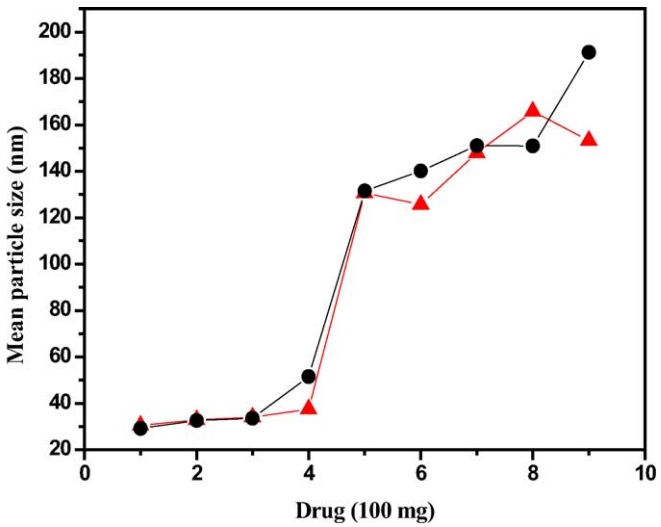

Fig. 2. Effect of the drug concentration on the droplet size in different media; distilled water (-●-) and simulated gastric fluid (-▲-).

3.4. In vitro dissolution study

Dissolution studies were performed for SMEDDS A-form, SMEDDS D-form, and the conventional tablet (Zocor®). The release of simvastatin from these dosage forms was evaluated in simulated intestinal fluid (pH 6.8); the release percentage of simvastatin from the SMEDDS form was significantly higher than that of simvastatin from the conventional tablet (Fig. 3). It could suggest that simvastatin dissolved perfectly in SMEDDS form could be released due to the small droplet size, which permits a faster rate of drug release into aqueous phase, faster than conventional tablet, including unsolubilized simvastatin, and it could affect the bioavailability. The release rate of simvastatin from SMEDDS A-form (mean droplet size: 33 nm) was faster than SMEDDS D-form (mean droplet size: 150 nm). So increasing the particle size of microemulsion could decrease the release rate of drug and it might suggest that release rate of drug could be controlled by regulating the mean particle size.

3.5. Bioavailability study

Based on the self-emulsification properties, particle size data, and stability of microemulsion, the formulation of Capryol 90, Carbitol, and Cremophor EL were selected for bioavailability studies. The in vivo study was performed to quantify simvastatin acid after administration of simvastatin. The plasma profiles of simvastatin in beagle dogs following oral administration of the conventional tablet and SMEDDS form were compared. Fig. 4 showed that plasma concentration profiles of simvastatin acid for SMEDDS A-form represented significantly greater improvement of drug absorption than the conventional tablet. Pharmacokinetic parameters of the maximum plasma concentration (C_{max}) and the corresponding time (T_{max}) for simvastatin acid following oral administration were shown in Table 3. The area under the concentration–time curve ($AUC_{0\rightarrow 24\,h}$) was estimated according to the linear trapezoidal rule. The relative bioavailability (BA) of SMEDDS form to the conventional tablet was calculated using the following equation:

$$\text{Relative BA (\%)} = \frac{AUC_{test}}{AUC_{reference}} \times \frac{Dose_{reference}}{Dose_{test}}$$

In pharmacokinetic parameters of SMEDDS A-form, $AUC_{0\rightarrow 24\,h}$ and C_{max} were 123.75±25.40 ng h/ml and 35.35 ± 8.22 ng/ml, respectively, compared with the conventional tablet (Zocor®, simvastatin 20 mg) which were 77.88±21.28 ng h/ml and 18.19±7.01 ng/ml, respectively, and the relative bioavailability of SMEDDS A-form to the conventional tablet was 159%. The absorption of simvastatin acid from SMEDDS A-form

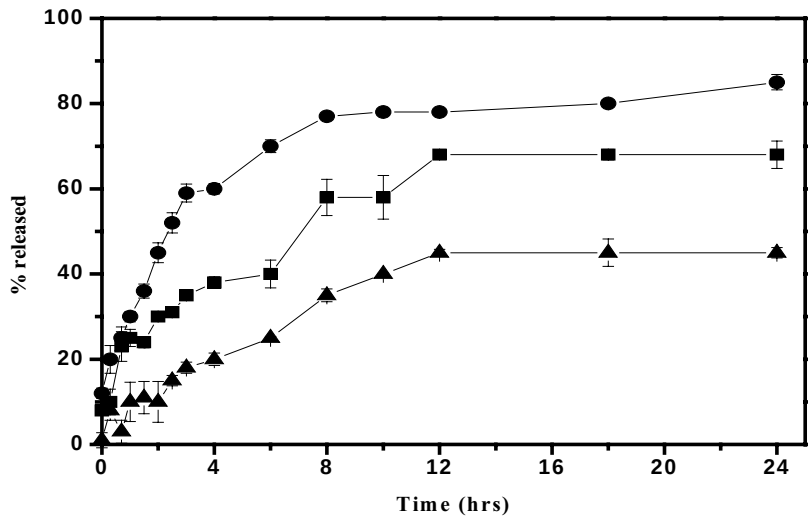

Fig. 3. Dissolution profiles of simvastatin from SMEDDS A-form (-●-), D-form (-■-), and the conventional tablet (-▲-).

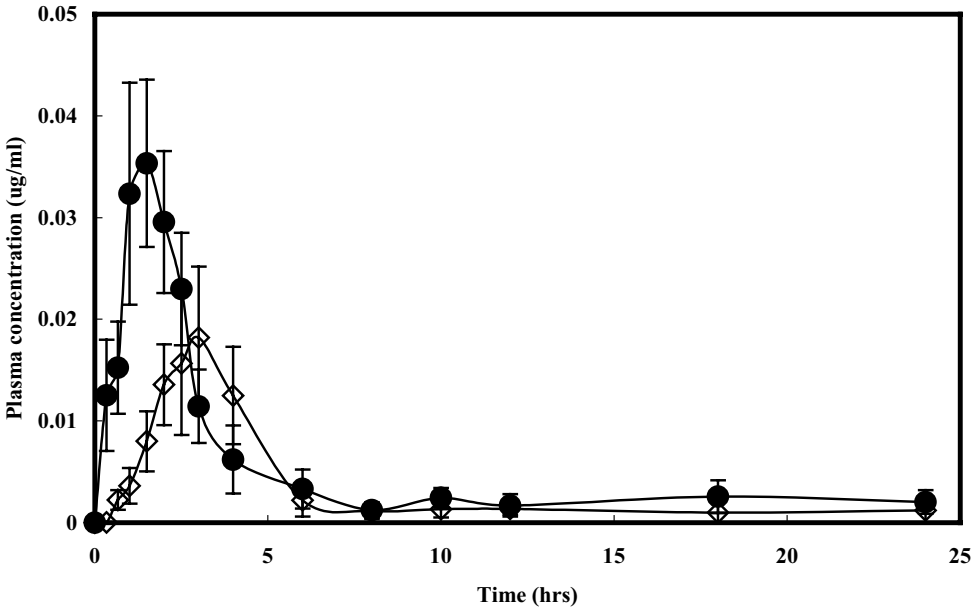

Fig. 4. Plasma concentration profiles of simvastatin acid after oral administration of the conventional tablet (-◇-) and SMEDDS A-form (-●-) in the beagle dogs ($n = 9$ and 2 mg/kg).

resulted in a 1.5-fold increase in bioavailability compared with the conventional tablet. The values of $AUC_{0\rightarrow 24\,h}$ and C_{max} and relative bioavailability of SMEDDS D-form were 111.25 ± 28.62 ng h/ml, 33.45 ± 11.50 ng/ml, and 143%, respectively. SMEDDS form enhanced the values of $AUC_{0\rightarrow 24\,h}$ and C_{max} of drug compared with the conventional tablet. Each T_{max} of SMEDDS forms A and D showed the fairly rapid onset compared with the conventional tablet. Therefore, SMEDDS might be a promising approach for the rapid onset and the effective absorption into oral administration delivery of simvastatin and could increase bioavailability for the other poorly water-soluble drug. T_{max} of SMEDDS A-form and D-form was 1.54 ± 0.30 h and 1.88 ± 0.35 h, respectively. This difference might be explained by the mean particle size of microemulsion from SMEDDS A-form (mean droplet size: 33 nm) and D-form (mean droplet size: 150 nm). The values of $AUC_{0\rightarrow 24\,h}$ of SMEDDS forms A and D were 123.75 ± 25.40 ng h/ml and 111.25 ± 28.62 ng h/ml, respectively. The spontaneous formulation of an emulsion upon drug release in the GI tract advantageously presents the drug in a solubilized form, and the small droplet size provides a large interfacial surface area for drug absorption (Charman et al., 1992; Shah et al., 1994).

Table 3
Relative bioavailability and pharmacokinetic parameters of simvastatin acid when simvastatin dosage forms were orally administered into the beagle dogs ($n = 9$, mean ± S.D.)

	Conventional tablet	SMEDDS A-form	SMEDDS D-form
Parameter			
$AUC_{0\rightarrow 24\,h}$ (ng h/ml)	77.88 ± 21.28	123.75 ± 25.40	111.25 ± 28.62
C_{max} (ng/ml)	18.19 ± 7.01	35.35 ± 8.22	33.45 ± 11.50
T_{max} (h)	2.81 ± 0.56	1.54 ± 0.30	1.88 ± 0.35
Relative bioavailability (%)	–	158.90	142.85

4. Conclusion

The optimal formulation of SMEDDS containing simvastatin (high drug loading and small particle size) was as following: Capryol 90 of 37%, Cabitol of 28%, and Cremophor EL of 28% due to high affinity for the continuous phase and forming the smallest particle size. In vitro dissolution studies revealed that release of simvastatin from SMEDDS was faster than the conventional tablet (Zocor®). Also, in vivo studies for clinical purpose, SMEDDS showed significantly greater extent of absorption than the conventional tablet. The relative bioavailability of SMEDDS A-form (33 nm size) and SMEDDS D-form (150 nm size) to the conventional tablet (Zocor®, simvastatin 20 mg) was 159 and 143%, respectively. Our studies illustrated the potential use of SMEDDS for the delivery of hydrophobic compounds, such as simvastatin, by the oral route.

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References

Aungst, B.J., 1993. Novel formulation strategies for improving oral bioavailability of drugs with poor membrane permeation or presystemic metabolism. J. Pharm. Sci. 82, 979–987.

Burcham, D.L., Maurin, M.B., Hausner, E.A., Huang, S.M., 1997. Improved oral bioavailability of the hypocholesterolemic DMP 565 in dogs following oral dosing in oil and glycol solutions. Biopharm. Drug Dispos. 18, 737–742.

Charman, S.A., Charman, W.N., Rogge, M.C., Wilson, T.D., Dutko, F.J., Pouton, C.W., 1992. Self-emulsifying drug delivery systems: formulation and biopharmaceutical evaluation of an investigational lipophilic compound. Pharm. Res. 9, 87–93.

Cheng, H., Sutton, S.C., Pipkin, J.D., Zentner, G.M., Rogers, J.D., Schwartz, J.I., Mitchel, Y.B., Grasing, K., Schwartz, M.S., Amin, R.D., Liu, L., Ebel, D.L., Coulter, A., Engle, K., McClelland, G.A., Lui, C.Y., Rork, G.S., 1993. Evaluation of sustained/controlled-release dosage forms of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors in dogs and humans. Pharm. Res. 10, 1683–1687.

Constantinides, P.P., 1995. Lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects. Pharm. Res. 12, 1561–1572.

Craig, D.Q.M., Lievens, H.S.R., Pitt, K.G., Storey, D.E., 1993. An investigation into the physicochemical properties of self-emulsifying systems using low frequency dielectric spectroscopy, surface tension measurements and particle size analysis. Int. J. Pharm. 96, 147–155.

Craig, D.Q.M., Barker, S.A., Banning, D., Booth, S.W., 1995. An investigation into the mechanisms of self-emulsification using particle size analysis and low frequency dielectric spectroscopy. Int. J. Pharm. 114, 103–110.

Kararli, T.T., Needham, T.E., Grifæn, M., Schoenhard, G., Ferro, L.J., Alcorn, L., 1992. Oral delivery of a renin inhibitor compound using emulsion formulations. Pharm. Res. 9, 888–893.

Kommuru, T.R., Gurley, B., Khan, M.A., Reddy, I.K., 2001. Self-emulsifying drug delivery systems (SEDDS) of coenzyme Q_{10}: formulation development and bioavailability assessment. Int. J. Pharm. 212, 233–246.

McClelland, C.A., Stubbs, R.J., Fix, J.A., Pogany, S.A., Zentner, G.M., 1991. Enhancement of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor efficacy through administration of a controlled-porosity osmotic pump dosage form. Pharm. Res. 8, 873–876.

Myers, R.A., Stella, V.J., 1992. Systemic bioavailability of penclomedine (NSC-338720) from oil-in-water emulsions administered intraduodenally to rats. Int. J. Pharm. 78, 217–226.

Palin, K.J., Phillips, A.J., Ning, A., 1986. The oral absorption of cefoxitin from oil and emulsion vehicles in rats. Int. J. Pharm. 33, 99–104.

Schwendener, R.A., Schott, H., 1996. Lipophilic 1-beta-D-arabino-furanosyl cytosine derivatives in liposomal formulations for oral and parenteral antileukemic therapy in the murine L1210 leukemia model. J. Cancer Res. Clin. Oncol. 122, 723–726.

Serajuddin, A.T.M., Sheen, P.-C., Mufson, D., Bernstein, D.F., Augustine, M.A., 1988. Effect of vehicle amphiphilicity on the dissolution and bioavailability of a poorly water-soluble drug from solid dispersion. J. Pharm. Sci. 77, 414–417.

Shah, N.H., Carvajal, M.T., Patel, C.I., Infeld, M.H., Malick, A.W., 1994. Self-emulsifying drug delivery systems (SEDDS) with polyglycolysed glycerides for improving in vitro dissolution and oral absorption of lipophilic drugs. Int. J. Pharm. 106, 15–23.

Stella, V., Haslam, J., Yata, N., Okada, H., Lindenbaum, S., Higuchi, T., 1978. Enhancement of bioavailability of a hydrophobic amine antimalarial by formulation with oleic acid in a soft gelatin capsule. J. Pharm. Sci. 67, 1375–1377.

Toguchi, H., Ogawa, Y., Iga, K., Yashiki, T., Shimamoto, T., 1990. Gastrointestinal absorption of ethyl 2-chloro-3-(4-(2-methyl-2-phenylpropyloxy)phenyl)propionate from different dosage forms in rats and dogs. Chem. Pharm. Bull. 38, 2792–2796.

Wakerly, M.G., Pouton, C.W., Meakin, B.J., Morton, F.S., 1986. Self-emulsification of vegetable oil-nonionic surfactant mixtures: a proposed mechanism of action. ACS Symp. Ser. 311, 242–255.